Ibrutinib Efficacy, Safety, and Pharmacokinetics in Chinese Patients with Relapsed or Refractory Waldenström's Macroglobulinemia: A Multicenter, Single-Arm, Phase 4 Study

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ABSTRACT

Introduction: Waldenström's macroglobulinemia (WM) is a rare malignant B cell lymphoma which occurs in around 1–2% of all hematologic tumors. Ibrutinib was approved in China for WM on the basis of two global pivotal studies which enrolled no Chinese patients. The aim of this study was to determine the efficacy, safety, and pharmacokinetics of ibrutinib in Chinese patients with relapsed or refractory (r/r) WM.

Methods: This was an open-label, single-arm, multicenter phase 4 study conducted across five sites in China. Enrolled patients with clinico-pathological confirmed WM received ibrutinib 420 mg once daily orally until disease progression or unacceptable toxicity. The primary endpoint was major response rate (MRR, partial response [PR], or better) according to the modified consensus criteria from the Sixth International Workshop on WM.

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Results: Seventeen patients were enrolled; at data cutoff (March 19, 2022), MRR was 64.7% (90% confidence interval [CI] 42.0–83.4) and overall response rate was 100% (90% CI 83.8–100.0). One (5.9%) patient achieved very good PR, 10 (58.8%) achieved PR, and six (35.3%) achieved minor response. The median duration of response (PR or better) was 14.8 months (95% CI 10.8–not estimable [NE]). Median progression-free survival was 18.4 months (95% CI 12.9–NE). All patients experienced at least one treatment-emergent adverse event (TEAE) related to the study drug, and grade ≥ 3 TEAEs were reported in 13 (76.5%) patients. There were no TEAEs leading to dose reduction or death. The median model estimated maximum plasma concentration and area under the plasma concentration–time curve during 24 h after dosing at steady state were 40.5 ng/mL and 204 ng·h/mL, respectively.

Conclusions: Ibrutinib demonstrated durable responses in Chinese patients with r/r WM. Treatment was well tolerated with no new safety signals compared with the pivotal global studies. Ibrutinib exposure was also comparable between Chinese and non-Chinese patients.

Trial Registration: ClinicalTrials.gov identifier NCT04042376.

Key Summary Points

Why carry out this study?

Waldenström's macroglobulinemia (WM) is a rare lymphoma characterized by the infiltration of the bone marrow by lymphoplasmacytic cells that produce monoclonal immunoglobulin M. Ibrutinib was approved in China in November 2018 for the treatment of symptomatic WM on the basis of the PCYC-1118E and PCYC-1127-CA pivotal studies which included no Chinese patients.

This phase 4 study was conducted to evaluate the efficacy, safety, and pharmacokinetics of ibrutinib in Chinese patients with relapsed or refractory (r/r) WM in a clinical trial setting.

What was learned from this study?

Single-agent ibrutinib showed durable clinical response in patients with r/r WM who were treated for a median duration of 14.3 months.

The major response rate (defined as partial response or better) was 64.7%. Side effects were manageable. Overall, our data confirmed the clinical benefit of ibrutinib in the clinical trial setting, complementing that of real-world evidence in patients with r/r WM in China.

INTRODUCTION

Waldenström's macroglobulinemia (WM) is a rare malignant B cell lymphoma that is associated with an accumulation of clinical lymphoplasmacytic cells and monoclonal immunoglobulin M (IgM) secretion [1]. This disease accounts for around 1–2% of all hematologic tumors at an incidence of 3–4 per million people per year in the USA [2]. Treatment is recommended for symptomatic disease only [3, 4], and it includes chemotherapy, chemoimmunotherapy combinations, proteasome inhibitors, alkylating agents, and Bruton tyrosine kinase (BTK) inhibitors [3–6].

Ibrutinib is the first-in-class BTK inhibitor with proven efficacy in many B cell malignancies [7], including in treatment-naïve patients or those with relapsed or refractory (r/r) WM [6, 8–10]. Clinical data from two pivotal studies (PCYC-1118E and PCYC-1127-CA) demonstrated high response rates of up to 90.5% [6, 8], and this led to the approval of ibrutinib for WM by the US Food and Drug Administration and European Medicines Agency [11, 12]. In

November 2018, the China National Medical Product Administration also approved ibrutinib for the treatment of WM on the basis of the results of the two pivotal studies, although no Chinese patients were enrolled [6, 8]. This made ibrutinib the first drug approved and recommended in the latest Chinese guidelines for WM, either as a monotherapy in the first-line setting for patients with WM who are not eligible to receive chemoimmunotherapy or who have received at least one prior treatment, or in combination with rituximab [4].

Before ibrutinib was approved for WM in China, most patients with symptomatic disease were treated with rituximab either as a monotherapy or in combination with chemotherapy. While rituximab-based regimens have been effective in WM, most patients will eventually develop resistance to rituximab because of widespread and repeated use [13, 14]. In addition to the tolerability issues arising from traditional systemic chemotherapies, treatment outcomes in the later-line settings have been modest, with the estimated median progression-free survival (PFS) reported in a large retrospective study in European patients with WM at 23.0 months and 16.0 months in the second- and third-line settings, respectively [13]. Therefore, ibrutinib represents a valuable treatment option that could potentially provide long-term disease control with reduced toxicity especially for those who do not respond to rituximab-based treatment.

The purpose of this post-approval phase 4 study was to evaluate the efficacy and safety and characterize the population pharmacokinetics (popPK) of ibrutinib monotherapy in Chinese patients with r/r WM.

METHODS

Study Design

This study (WAL4001) was an open-label, single-arm, multicenter phase 4 study conducted at five study sites in China. Enrolled patients received ibrutinib orally at a dose of 420 mg once daily until disease progression or unacceptable toxicity. Patients who progressed on

treatment were followed up on subsequent anticancer therapy, occurrence of other malignancy, survival status recorded until death, loss of follow-up, consent withdrawal, or study closure. The study protocol was amended once on March 25, 2020, to update the safety information regarding cerebrovascular incidence identified in the post-marketing setting and to clarify procedures and the collection of data.

This study was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and local applicable regulatory requirements. All patients provided written informed consent according to the local requirements prior to enrollment. The trial protocol and any amendments were reviewed and approved by an independent ethics committee at each investigation site (Supplementary Table S1). This trial is registered with ClinicalTrials.gov (NCT04042376).

Patients

Key eligibility criteria included ≥ 18 years of age with centrally confirmed clinicopathological diagnosis of WM in accordance with the consensus panel of the Second International Workshop on WM (IWWM) [15]. Enrolled patients must also have at least one prior therapy, documented disease progression, or had no response to the most recent treatment regimen, a symptomatic disease meeting at least one criterion from the Second IWWM requiring treatment, measurable disease defined as serum monoclonal IgM > 0.5 g/dL, hematology and biochemical values within protocol-defined limits, and an Eastern Cooperative Oncology Group performance status (ECOG PS) score of ≤ 2.

Patients were excluded from the study if they had known central nervous system involvement by WM, prior exposure to ibrutinib or other BTK inhibitors, hypersensitivity reaction to ibrutinib or to the excipients in its formulation, previously received WM-related therapy at most 30 days prior to first administration of the study treatment, received allogeneic hematopoietic stem cell transplant or plasmapheresis less than

35 days prior to the initiation of study treatment, history of stroke or intracranial hemorrhage within 6 months prior to enrollment, known bleeding disorders or hemophilia, or clinically significant cardiovascular disease, hepatic impairment, or active infection. A full account of the inclusion and exclusion criteria is described in Supplementary Table S2.

Outcomes and Assessments

The primary endpoint was major response rate (MRR, overall response rate was the term stated in the protocol) by investigator assessment, defined as the proportion of patients who achieved partial response (PR) or better according to the modified consensus criteria from the Sixth IWWM [16]. Secondary endpoints were overall response rate (ORR [clinical response rate was the term used in the protocol], defined as minor response [MR] or better), very good PR or better rate, duration of response (DOR), time to response (TTR), PFS, overall survival (OS), pharmacokinetics, and safety. All treatment responses were evaluated as per the Sixth IWWM by investigators [16]. The definitions of the efficacy endpoints are described in Supplementary Table S3.

Safety was evaluated on the basis of adverse events, clinical laboratory tests, physical examinations, and vital signs, summarized using frequencies and percentages. Adverse events were graded per National Cancer Institute Common Terminology Criteria for Adverse Events v4.03 and assessed from informed consent to 30 days after last dose of study drug. Adverse events of special interest defined by the sponsor (major hemorrhage event) were also reported. Patients were observed for any adverse events until 30 days after the last dose of study drug.

Baseline tumor assessment was performed up to 42 days before the first dose of treatment. Computed tomography (CT) scans of the neck, chest, abdomen, and pelvis were performed. Magnetic resonance imaging was allowed if the CT scans could not be used to evaluate the sites of disease adequately. Radiographic imaging was performed every 16 weeks for the first 2 years, and thereafter every 24 weeks until disease progression. Bone marrow aspirate and biopsy were required at screening. Bone marrow was required to confirm complete response (CR), pre-dose at weeks 49 and 97 to assess response, and at time of progression or suspected progression due to progressive cytopenia.

Disease progression based on changes in IgM levels determined either by serum protein electrophoresis or by a quantitative IgM serum immunoglobulin test was confirmed by a subsequent evaluation within at least 4 weeks of the first finding.

Blood samples were collected from all patients for the measurement of plasma concentrations of ibrutinib and the metabolite PCI-45227 before treatment on day 1 of weeks 1, 5, and 9. The pharmacokinetic-evaluable patients were defined as patients who received at least one dose of study drug and had at least one quantifiable pharmacokinetic sample obtained post-treatment.

Statistical Analysis

Sample size was determined with the assumption that MRR by investigator is 69.8% in the study population, similar to the study by Treon et al. [6]. Hence, approximately 17 patients were recruited to obtain a power of 85% and to achieve a clinically meaningful MRR of 32% or higher with a one-sided significance level of 0.05.

Efficacy and safety analyses were performed on all patients who received at least one dose of ibrutinib. Pharmacokinetics analyses were performed on all patients who received at least one dose of ibrutinib and had at least one available pharmacokinetic sample after treatment. MRR, ORR, and very good PR or better rate were calculated using exact binomial distribution, and the exact (Clopper-Pearson) 90% confidence intervals (CIs) are presented. Time to event variables (DOR, PFS, and OS) and the corresponding 95% CIs were described using the Kaplan–Meier method. Time to major response was summarized descriptively for responders. Observed plasma concentrations of ibrutinib and metabolite PCI-45227 were summarized

using descriptive statistics. Exposure matrices, including maximum plasma concentration at steady state (C_{max}) and area under the plasma concentration–time curve during 24 h after dosing at steady state ($AUC_{\tau,ss}$), of ibrutinib from this study and from the two pivotal studies (PCYC-1118E and PCYC-1127-CA) were derived using the individually predicted ibrutinib concentrations from popPK modeling.

PopPK Modeling

A popPK analysis was conducted to characterize the PK of ibrutinib in Chinese patients with WM after oral administration. This analysis included data from the current study and the other two global pivotal trials (PCYC-1118E and PCYC-1127-CA) [6, 8]. PK-evaluable patients were defined as those who received at least one dose of study drug and had at least one quantifiable PK sample obtained post-treatment. The concentrations of metabolite PCI-45227 were not included in the popPK analysis.

A popPK model for ibrutinib was first developed using data from patients with B cell malignancies [17]. This initial popPK model was further updated by including additional internal clinical studies in patients with B cell malignancies (updated model, not published) and has been used for this work. In the previous popPK analysis, ibrutinib concentrations could be described using a two-compartmental model with sequential zero to first-order absorption and first-order elimination. The model was parameterized in terms of relative bioavailability and zero to first-order absorption (duration of zero order input [D1], temporal delay [lag time] before absorption process is started [ALAG1], and first-order absorption rate constant [ka]), linear clearance (CL), volume of distribution in the central compartment (V2), intercompartmental clearance (Q), and volume of distribution in the peripheral compartment (V3) (Supplementary Fig. S1). Interindividual variability was modeled with an exponential term. Residual variability was described using an additive model, as the plasma ibrutinib concentrations were log-transformed. The effects of CYP3A inhibitors (taken or not taken)

and increasing age (continuous covariate) on F1 and meal condition (fast, modified fast, or fed) on D1 had been identified as statistically significant (but not clinically relevant) covariates for the final popPK model.

In this popPK analysis, the empirical Bayesian estimation (EBE) was performed using the previously developed model on the data from all three studies. In the EBE, basic goodness-of-fit plots were generated to assess the fit of the previous model on the current data, with the following graphs compared: observed concentrations versus population prediction (PRED), observed concentrations versus individual prediction (IPRED), conditional weighted residual (CWRES) versus PRED, and CWRES versus time since first dosing. In addition, a visual predictive check (VPC) was also performed to evaluate the agreement between the observed and predicted concentration generated by the previous popPK model. After we demonstrated that the previous model could describe the current data, the exposure metrics (C_{max} and $AUC_{\tau,ss}$) at the recommended dose schedule (420 mg orally once daily) were derived from the predicted ibrutinib concentrations using the individual parameters obtained in the EBE for the three studies. The derived exposure metrics were compared between Chinese patients in the WAL4001 study and non-Chinese patients in the PCYC-1118E and PCYC-1127-CA studies. The analysis was conducted using a nonlinear mixed-effects model analysis in NONMEM® (Version 7.4, Icon Development Solutions, Ellicott City, MD).

In the final dataset, a total of 546 (WAL4001, 31; PCYC-1118E, 62; PCYC-1127-CA, 453) post-dose quantifiable samples of ibrutinib concentrations from 126 (WAL4001, 17; PCYC-1118E, 16; PCYC-1127-CA, 93) PK-evaluable patients were included in the popPK analysis.

RESULTS

Patient Demographics and Baseline Characteristics

Seventeen patients were enrolled, and their detailed demographics and characteristics are

Table 1 Baseline demographics and patient characteristics

Characteristics	Ibrutinib 420 mg (N = 17)
Median age at enrollment, years (range)	64.0 (50.0–79.0)
Sex	
Female	7 (41.2)
Male	10 (58.8)
Time since initial diagnosis, months	
Median (range)	46.7 (1.5–122.0)
ECOG PS	
0–1	15 (88.2)
2	2 (11.8)
Median serum IgM, g/L (range)	44.5 (15.5–85.5)
Median β2-microglobulin, mg/L (range)	3.6 (1.7–9.5)
Median total M-protein, g/L (range)	25.0 (8.0–66.0)
Median hemoglobin, g/L (range)	95.0 (60.0–153.0)
Median platelets count, 10^9/L (range)	224.0 (81.0–380.0)
Median absolute neutrophil count, 10^9/L (range)	3.4 (0.9–9.7)
Median sum of products of diameters, mm^2 (range)	2363.0 (305.0–6417.0)
Extramedullary disease[a]	12 (70.6)
Adenopathy	11 (64.7)
Splenomegaly	2 (11.8)
Bone marrow involvement, %	
Median cellularity[b] (range)	65 (40–85)
Median intertrabecular space[b] (range)	60 (0–85)
Number of prior systemic therapies	
1–2	12 (70.6)
≥ 3	5 (29.4)
Common (> 15%) prior WM-related systemic therapy	
Cyclophosphamide	12 (70.6)

Table 1 continued

Characteristics	Ibrutinib 420 mg (N = 17)
Rituximab	12 (70.6)
Dexamethasone	11 (64.7)
Bortezomib	10 (58.8)
Thalidomide	7 (41.2)
Prednisone	6 (35.3)
Dexamethasone sodium phosphate	4 (23.5)
Pirarubicin hydrochloride	3 (17.6)
Vincristine	3 (17.6)
Vindesine	3 (17.6)

Unless otherwise stated, data are n (%)

ECOG PS Eastern Cooperative Oncology Group performance status, *IgM* immunoglobulin M, *WM* Waldenström's macroglobulinemia

[a] Adenopathy was defined as any target lymph nodes with a long axis of > 1.5 cm or a short axis of > 1.0 cm, and splenomegaly was defined as a spleen depth (cranial to caudal) of > 13 cm

[b] Assessed using bone marrow pathology/immunohistochemistry

summarized in Table 1. The median age was 64 (50–70) years; 10 (58.8%) were male. The majority of patients had an ECOG PS of 0 or 1 (n = 15, 88.2%), a serum IgM level of ≤ 70 g/L (n = 15, 88.2%), and extramedullary disease (n = 12, 70.6%). Median sum of products of diameters (SPD) for the target nodal lesions was 2363.0 mm^2 (n = 11; 305.0–6417.0). Median baseline hemoglobin was 95.0 g/L (60–153), and 10 (58.8%) patients had hemoglobin ≤ 110 g/L. All patients received at least one prior systemic therapy for WM (1–4), and five (29.4%) received at least three prior systemic therapies. Glucocorticoids (n = 17, 100%) and nitrogen mustard analogues (n = 13, 76.5%) were the most common prior WM-related systemic therapeutic medication class used. Other systemic medication classes used included monoclonal

antibodies ($n = 12$, 70.6%), proteasome inhibitors ($n = 10$, 58.8%), vinca alkaloids and analogues ($n = 10$, 58.8%), and other immunosuppressants ($n = 9$, 52.9%) such as thalidomide and lenalidomide. The complete list of systemic therapy used is presented in Supplementary Table S4. The most common prior treatment regimens were bortezomib, dexamethasone, and rituximab (BDR, $n = 5$); bortezomib and dexamethasone (BD, $n = 3$); dexamethasone, rituximab, and cyclophosphamide (DRC, $n = 3$); and cyclophosphamide, vindesine, prednisone, and rituximab (CVP-R, $n = 3$). One (5.9%) patient received prior WM plasmapheresis.

At data cutoff (March 19, 2022), eight patients remained on treatment (Fig. 1). Five (29.4%) patients discontinued treatment because of adverse events, three (17.6%) due to progressive disease, and one (5.9%) withdrew consent. Median duration of treatment was 14.3 months (2.5–22.2) and median follow-up time was 15.7 months (5.7–23.1).

Efficacy

At the time of data cutoff, the MRR was 64.7% (90% CI 42–83.4; Table 2). The primary efficacy endpoint of MRR prespecified as $\geq 32\%$ of the lower limit of the 90% CI was met. One (5.9%) patient achieved very good PR and 10 (58.8%) achieved PR, six (35.3%) of whom achieved MR. All patients achieved MR or better response. The
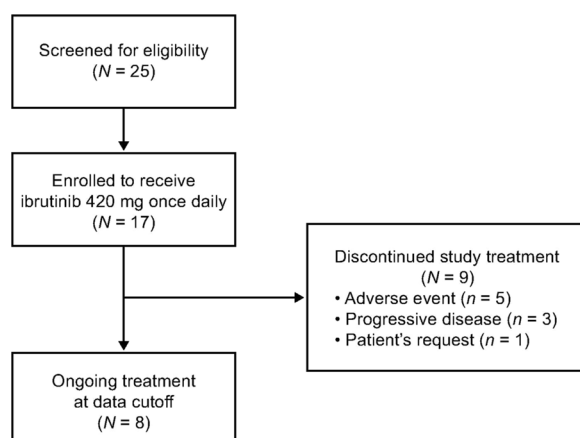
Fig. 1 Patient disposition

Table 2 Investigator-assessed efficacy outcomes

	Ibrutinib 420 mg ($N = 17$)
Best overall response, n (%)	
Complete response	0
Very good partial response	1 (5.9)
Partial response	10 (58.8)
Minor response	6 (35.3)
Stable disease	0
Progressive disease	0
Not evaluable	0
Unknown	0
Major response rate[a]	11 (64.7)
90% CI[b]	42–83.4
Overall response rate[c]	17 (100.0)
90% CI[b]	83.8–100
Very good partial response or better rate	1 (5.9)
90% CI[b]	0.3–25.0
Median duration of response, months[d]	14.8
95% CI[e]	10.8–NE
Median time to major response, months[f]	3.7
95% CI[e]	1.8–3.7
Median time to overall response, months[g]	0.95
95% CI[e]	0.95–1.81
Median progression-free survival, months	18.4
95% CI[e]	12.9–NE
Median overall survival, months	NE

Table 2 continued

	Ibrutinib 420 mg (N = 17)
95% CI[e]	13.5–NE

Unless otherwise stated, data are n (%)

CI confidence interval, NE not estimable

[a]Major response rate was defined as patients who achieved complete response, very good partial response, or partial response

[b]90% CI was calculated using the Clopper-Pearson exact method

[c]Overall response rate was defined as patients who achieved minor response or better

[d]Duration of response was defined as duration from the date of initial documentation of a response (partial response or better) to the date of first documented evidence of progressive disease, death, or date of censoring if applicable, for responders (partial response or better) as assessed by the investigator. Duration will be censored at the date of last adequate disease assessment showing no evidence of disease progression

[e]Based on Kaplan–Meier estimates

[f]Time to response was calculated as the number of months from the first dosing date of ibrutinib to the first documented response for patients who achieved partial response or better

[g]Time to overall response was calculated as the number of months from the first dosing date of ibrutinib to the first documented response for patients who achieved minor response (i.e., at least a 25% but < 50% reduction of serum IgM from baseline) or better

ORR was 100% (90% CI 83.8–100%). The median DOR among those who achieved PR or better was 14.8 months (95% CI 10.8–not estimable [NE]; Fig. 2a). Median time to major response was 3.7 months (95% CI 1.8–3.7) and median time to overall response was 0.95 months (95% CI 0.95–1.81). IgM improvement was observed in all patients (Supplementary Fig. S2). Treatment with ibrutinib resulted in a rapid reduction in serum IgM which continued over time throughout the study (Supplementary Fig. S3). At week 49, the median IgM levels were reduced by 68.4% (19.0–89.2%). The patient with very good PR recorded a maximum improvement from baseline in IgM levels by 91.4% at week 51. By week 33, SPD reduction was observed in the majority of patients (n/N = 9/11, 81.8%) with adenopathy at baseline. The median SPD was reduced by 57.8% (23.9–77.6%) and the maximum reduction in SPD from baseline was 80.0% at week 49, which was observed in a patient who achieved PR as best overall response.

Six (35.3%) patients had events of disease progression or death. Median PFS was 18.4 months (95% CI, 12.9–NE; Fig. 2b) and the 12 month PFS rate was 94% (95% CI 63–99). The median OS was not reached (95% CI 13.5–NE; Supplementary Fig. S4); 18-month OS rate was 84% (95% CI 49–96). Two deaths were reported during the study; one was due to pneumonia, which occurred more than 30 days after the last dose of study treatment and therefore was not considered related to treatment, and the reason for the other death was unknown (patient's family declined to provide the cause of death).

Safety

All patients experienced at least one treatment-emergent adverse event (TEAE; Table 3) and treatment-related adverse event (Supplementary Table S5). Grade 3 or higher TEAEs and serious TEAEs were reported in 13 (76.5%) and eight (47.1%) patients, respectively. No TEAEs leading to death or dose reduction of ibrutinib were reported. Dose interruption was reported in three (17.6%) patients and due to arrhythmia (n = 1), ureterolithiasis (n = 1), and hypercalcemia and fracture (n = 1). Five (29.4%) patients discontinued treatment as a result of TEAEs.

The most frequently reported TEAEs (> 10% of patients) are presented in Table 3, and they included hyperuricemia (n = 11, 64.7%); neutrophil count decreased and white blood cell count decreased (both n = 5, 29.4%); hypoalbuminemia, upper respiratory tract infection, eczema, and anemia (all n = 4, 23.5%); and platelet count decreased, weight increased, and upper abdominal pain (all n = 3, 17.6%). Grade ≥ 3 TEAEs were reported in 13 (76.5%) patients; the most frequently reported grade
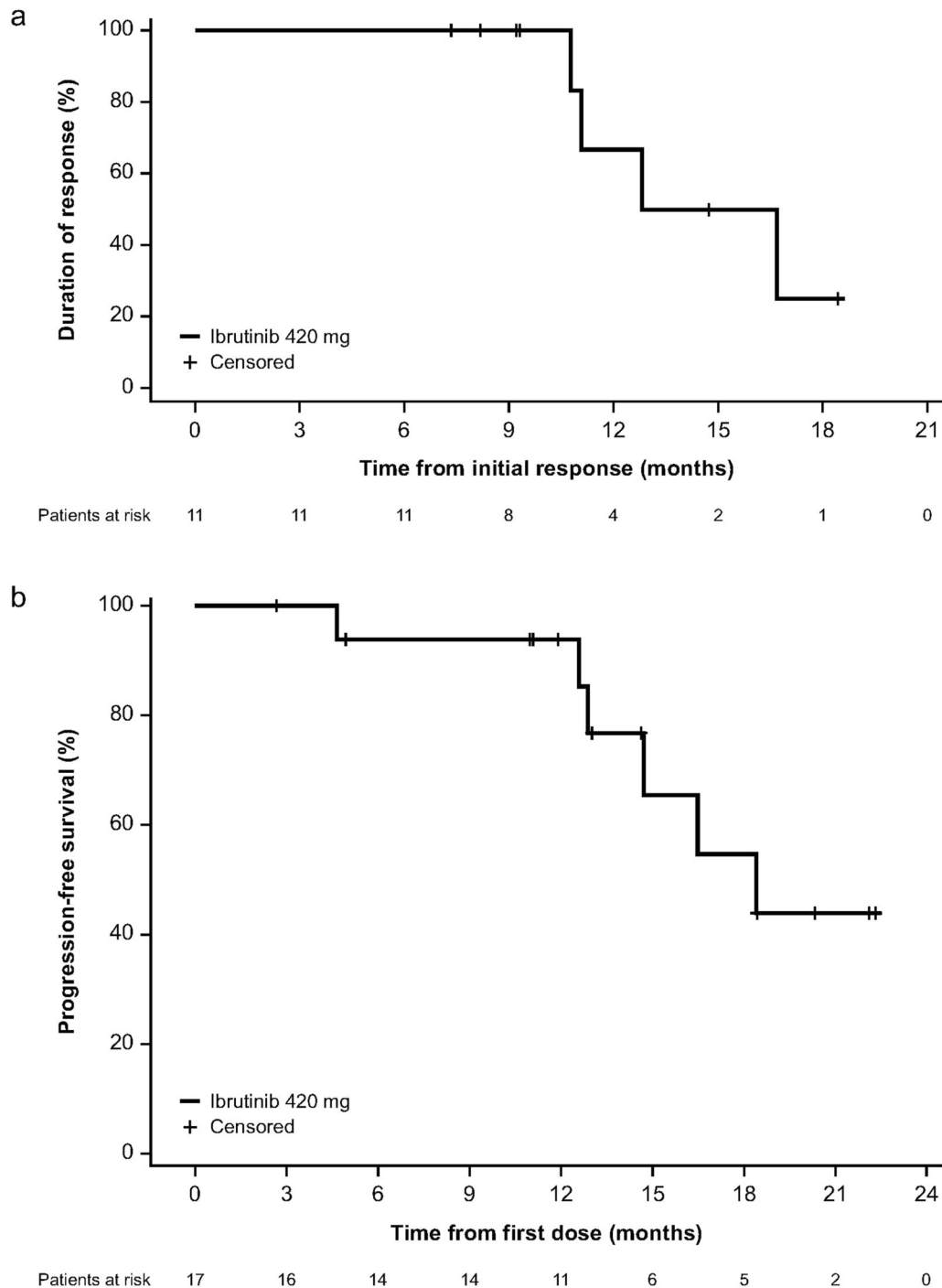
Fig. 2 Kaplan–Meier curves for **a** duration of response and **b** progression-free survival

≥ 3 TEAEs were hyperuricemia ($n = 5$, 29.4%), neutrophil count decreased ($n = 3$, 17.6%), and anemia ($n = 2$, 11.8%). Serious adverse events (SAEs) were reported in eight (47.1%) patients.

One (5.9%) patient reported an adverse event of special interest, which was grade 4 major hemorrhage intracranial, resulting in ibrutinib discontinuation. In terms of cardiac events, one

Table 3 Most common treatment-emergent adverse events (at least 10%)

	Ibrutinib 420 mg[a,b]	
	All grade	Grade ≥ 3
Patients with one or more TEAE	17 (100.0)	13 (76.5)
Hyperuricemia	11 (64.7)	5 (29.4)
Neutrophil count decreased	5 (29.4)	3 (17.6)
White blood cell count decreased	5 (29.4)	0
Hypoalbuminemia	4 (23.5)	0
Upper respiratory tract infection	4 (23.5)	0
Eczema	4 (23.5)	0
Anemia	4 (23.5)	2 (11.8)
Platelet count decreased	3 (17.6)	1 (5.9)
Weight increased	3 (17.6)	0
Upper abdominal pain	3 (17.6)	0
Hyperglycemia	2 (11.8)	0
Hypokalemia	2 (11.8)	0
Herpes zoster	2 (11.8)	0
Pneumonia	2 (11.8)	1 (5.9)
Diarrhea	2 (11.8)	0
Rash	2 (11.8)	0

TEAE treatment-emergent adverse event

[a]Patients were counted only once for any given event, regardless of the number of times they experienced the event

[b]Adverse events were coded using MedDRA version 24.1

patient experienced grade 2 cardiac failure which resulted in treatment discontinuation, and another had grade 2 cardiac arrhythmia which led to dose interruption. New malignancy was reported as an adverse event of clinical interest, and in our study, lung squamous cell carcinoma presented in one patient which also resulted in treatment discontinuation.

No clinically meaningful changes were observed in vital signs (blood pressure, weight, heart rate, respiratory rate, and body temperature). One patient reported abnormal values for electrocardiogram, reported as grade 2 arrythmia, resulting in dose interruption.

Pharmacokinetics Based on Observed Data

The median concentration of ibrutinib and its metabolite PCI-45227 on day 1 of week 5 was 1.71 ng/mL (range, below quantification limit to 12.7 ng/mL) and 7.79 ng/mL (1.74–85.8 ng/mL), respectively. The median concentration of ibrutinib and its metabolite PCI-45227 on day 1 of week 9 was 2.71 ng/mL (0.708–26.2 ng/mL) and 13.3 ng/mL (1.80–113 ng/mL), respectively.

PopPK Analysis

The goodness-of-fit plots for all three studies showed that CWRES values were generally scattered around the zero line across predicted range and time, while population predictions deviated from the identity line in WAL4001, likely as a result of the small sample size (Supplementary Fig. S5). VPC appeared to capture the central tendency and variability of the observed data (Supplementary Fig. S6). These results of external model evaluation indicated the consistency of ibrutinib PK profiles after oral administration in patients with WM and patients with other hematological malignancies, and between Chinese and non-Chinese patients with WM. The predicted median (range) C_{max} and $AUC_{\tau,ss}$ were 40.5 ng/mL (28.7–90.4 ng/mL) and 204 ng·h/mL (133–507 ng·h/mL), respectively, in WAL4001 (Supplementary Table S6).

DISCUSSION

To our knowledge, this phase 4, single-arm, multicenter study is the first sponsor-initiated clinical trial to evaluate the clinical benefit of ibrutinib in Chinese patients with r/r WM, a population not included in previous pivotal ibrutinib clinical trials. Our study showed that the use of once-daily, single-agent ibrutinib afforded an MRR (defined as PR or better) of

64.7% per the modified Sixth IWWM criteria, with a median DOR of 14.8 months. One patient achieved very good PR and 10 had a PR. After a median follow-up of 15.7 months, median PFS was 18.4 months and median OS was not reached.

Our study results showed similar trends in terms of treatment responses and survival outcomes to previous pivotal studies. In a large phase 2 open-label study (PCYC-1118E), 63 previously treated patients who received ibrutinib monotherapy for a median duration of 19.1 months had a major response rate (defined as PR or better) of 73% and an ORR (defined as MR or better) of 90.5% [6]. After a median follow-up of 59 months, overall and major response rates were 90.5% and 79.4%, respectively [10]. The median 5-year PFS rate was 54%, and the 5-year OS rate was 87% [10]. In the phase 3 open-label substudy of the iNNOVATE trial by Dimopoulos et al. (PCYC-1127-CA), ibrutinib monotherapy demonstrated efficacy in 31 pretreated (rituximab-refractory) patients with WM, reporting an ORR (defined as MR or better) of 90% and major response rate (defined as PR or better) of 71% after a median follow-up of 18.1 months [8]. The estimated 18-month PFS and OS rates were 86% and 97%, respectively [8]. A more recent update on the final analysis of the iNNOVATE substudy with up to 5 years of follow-up indicated sustained treatment response, with ORR at 87% and 29% and 48% of patients achieving a very good PR and PR, respectively [14]. The median PFS and OS were 39 months and not reached, respectively [14]. In the present study, MRR, defined as PR or better, was similar to that observed in the previous pivotal studies. ORR, defined as MR or better, was higher, but the very good PR or better rate was lower than that in the pivotal studies, and this could be attributed to the higher disease burden of patients at baseline. Of note, patients enrolled in our study had higher serum IgM and lower hemoglobin levels at baseline compared with the other two pivotal studies; the incidence of extramedullary disease was similar but SPD among those with adenopathy was higher in the present study [6, 8].

Time to major response in the present study was 3.71 months, slightly longer than in both pivotal studies [6, 8]. Firstly, this could be attributed to the adoption of the latest Sixth IWWM guidelines on response criteria, requiring not only a reduction in IgM levels but also in extramedullary disease to be considered PR or better response. Unlike in the Third IWWM criteria that was adopted in the study by Treon and colleagues [6], a reduction of IgM levels by 50% would constitute a PR or better response. Moreover, 12 of the patients in our study who had extramedullary disease at baseline underwent their first image assessment on week 17 as per protocol, thereby delaying the confirmation of treatment response. Of note, time to overall response was 0.95 months, indicating an initial early response to ibrutinib of less than a month was achieved among Chinese patients.

Based on the results of this popPK analysis, the predicted median C_{max} and $AUC_{\tau,ss}$ at the recommended dose schedule (420 mg orally once daily) in Chinese patients in the WAL4001 study was numerically lower but generally within the range of the results in non-Chinese patients in global studies PCYC-1118E and PCYC-1127-CA (Supplementary Table S6 and Fig. S7). This indicates the consistency in the PK characteristics between Chinese and non-Chinese patients with WM after daily oral administration of ibrutinib.

Overall, ibrutinib was well tolerated, and no new safety signals emerged among Chinese patients. The incidence of TEAEs, drug-related TEAEs, and SAEs was similar across all three studies [6, 8]. However, TEAEs leading to treatment discontinuation occurred at a rate higher in our study than in the other two pivotal trials [6, 8]. We also observed a higher incidence of metabolism and nutritional disorders, but fewer gastrointestinal disorders. The incidence and severity of hyperuricemia observed in our study were also higher than in the other pivotal trials. Majority of those patients recovered at data cutoff without impacting the study. Rare cases of atrial fibrillation previously reported in other studies with ibrutinib were not observed here [6, 9, 10]. There was a single case of cardiac arrythmia which was resolved through dose interruption. Both cardiac conditions are not

practice-altering as they could be managed with dose modification or the use of other pharmacological agents.

Small sample size is a limitation of our study, which was calculated on the basis of the objective of achieving a clinically meaningful MRR of 32% or higher. Patient genomic profiling was not assessed in our study, which could otherwise provide additional data on the impact of tumor genotypes on treatment outcomes in Chinese patients, given that the clinical response to ibrutinib could be influenced by *MYD88* and *CXCR4* genotypes [6, 14]. Further study is warranted with a longer duration of follow-up to understand the other prognostic factors, such as age, prior lines of systemic therapy, International Prognostic Scoring System for Waldenström Macroglobulinemia score, among others, to inform treatment outcomes. A study recently reported the long-term outcomes of ibrutinib monotherapy in WM [18]. Although the patient population was treatment-naïve, after a median follow-up of 50 months, MRR was 87% and 4-year PFS rate was 76%, signaling that ibrutinib was well tolerated and can provide long-term disease control [18].

CONCLUSION

Ibrutinib monotherapy was active and showed durable responses in Chinese patients with r/r WM, consistent with previous studies. The exposure of ibrutinib was generally comparable between Chinese and non-Chinese patients with WM. The study met its primary endpoint and treatment was well tolerated with no new safety signals, reaffirming ibrutinib as an ideal treatment option for WM in China.

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Data Availability. The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

Declarations

Conflict of Interest. Lugui Qiu receives consultation fees and honoraria from Xian Janssen Pharmaceutical Ltd, Pfizer, Beigene, and Roche. Qian Li, Linlin Sha, Nating Zhang, Yupeng Ren, Xue Gai, Xue Yang, and Rui Qin are employees of Johnson & Johnson. Xue Yang and Rui Qin report stock ownership from Johnson & Johnson. Shuhua Yi, Yu Hu, Zhen Cai, Aili He, and Sujun Gao have nothing to disclose.

Ethical Approval. This study was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and local applicable regulatory requirements. All patients provided written informed consent according to the local requirements prior to enrollment. The trial protocol and any amendments were reviewed and approved by an independent ethics committee at each investigation site.

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